REMARKS

I. Status of the Claims

Claims 1-31 were filed with the application. Claims 2, 3, 5-8 and 10-31 have been withdrawn from consideration. Thus, claims 1, 4 and 9 are under consideration and have been examined. The claims are rejected under 35 U.S.C. §112, first paragraph (enablement).

II. Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 1, 4 and 9 remain rejected for alleged lack of enablement. Claim 1 is considered a linking claim for all canceled claims and arguments presented herein address all of the claims at issue.

Applicants previously argued that the examiner was applying an inappropriately high standard for enablement, tantamount to requiring working examples in humans. Those arguments are maintained an reiterated in light of the McKinsey Declaration (attached). The examiner again disagrees, and sums up his position by stating that "From the evidence of record, since multiple pathways exist that end in a hypertrophic state lacking any clear and distinct role for MEF2 in all these pathways ... one would conclude that simply inhibiting MEF2 will have no effect." Applicants traverse this notion.

Examples 3 and 6 clearly show that MEF2 is activated in response to hypertrophic signals. As stated in these examples, MEF2 would be considered an endpoint in the hypertrophic cascade. Admittedly, while it may be theoretically difficult to treat a disease by targeting a single cellular pathway, MEF2 is a downstream effector of the hypertrophic cascade, a gateway as it were for a variety of cascades and agonists that lead to the development of hypertrophy as

signaled by up regulation of MEF2 dependent genes. The activation of MEF2 dependent "fetal" genes is seen in virtually all known forms of pathological cardiac hypertrophy. Thus, inhibiting the role of MEF2 would be expected to benefit patients suffering from hypertrophic response to cardiac insult by a variety of hypertrophic agonists.

Further, as explained in the attached declaration of Dr. Timothy McKinsey (erroneously omitted from the previous submission), the binding activity referred to in Example 6 of the instant application is crucial in the regulation of MEF2 dependent genes, and targeting this interaction has shed further light both on the activity of MEF2 as well as the ability of one to inhibit hypertrophy by inhibiting the activity of MEF2. The inventors have shown that MEF2 associates with class II HDAC's, as demonstrated in the inventor's own U.S. Patent 6,632,628 and U.S. Patent 6,707,686. As shown therein, as well as in Zhang *et al.* (2002), and McKinsey *et al.* (2002), the MEF2-class II HDAC interaction is a critical, necessary and sufficient interaction for the regulation of hypertrophy. Ablation of this interaction is deleterious to the heart. Both overexpression of class II HDACs and sequestering of HDACs in the nucleus are profoundly anti-hypertrophic, rendering cells not only resistant to hypertrophic stimuli, but actually reversing hypertrophy once it has begun. Knocking out HDACs - in essence eliminating the cellular regulatory molecule for MEF2 - leads to profound and rapid development of hypertrophy (see Zhang *et al.*, 2002).

The examiner argues against this interpretation, stating that the cited art suggests only ***possible*** effects from inhibiting MEF2, and that other targets (*e.g.*, HDACs) are preferred. However, these conclusions are directly refuted by the declaration of Dr. McKinsey. Furthermore, whether a target is a more or less preferred target is irrelevant to whether it is a ***viable*** therapeutic target. Zhang (2002) does not state that MEF2 is an impossible or futile target

for developing cardiac therapies, Zhang merely states that HDAC's are a newly discovered and exciting target for therapy. The conclusions of Zhang, that "class II HDACs and their regulatory kinases(s) appear to represent a [downstream] point of convergence [in the hypertrophic cascade] and as such represent *potential* therapeutic targets (emphasis added)" actually supports targeting MEF2, which is equally downstream in the cascade and is therefore far less likely to create problems often seen in targeting effector molecules higher up in any signaling cascade.

Further, the examiner argues that Olson (2004) states that the link between MEF2 endothelial disorders is not proven. Cardiac hypertrophy is ***not*** an endothelial cell disorder. The only reference to cardiac tissue in the cited passage from Olson is related to indirect vascular effects:

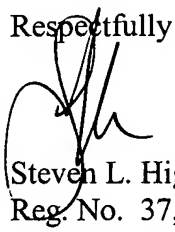
> The vascular endothelium is a seamless, yet dynamic, tissue required for multiple functions of the cardiovascular system, including maintenance of vascular tone, regulation of blood circulation, coagulation, inflammatory responses, and proper growth and development of vascular smooth muscle and cardiac myocytes. Perturbation of the vascular endothelium is responsible for a variety of cardiovascular disorders, including atherosclerosis, thrombosis, and hypertension.

Thus, applicant again asserts that, in light of the discussion above and the attached affidavit, the rejected claims are in fact enabled by the instant specification. Therefore, it is respectfully requested that the claims be reconsidered and the rejection be withdrawn.

III. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Woitach have any questions regarding this response, she is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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